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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
EINSMANN, JULIET CAROLINE

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,373	SHULDINER ET AL.	
	Examiner	Art Unit	
	Juliet Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 2, and 7, drawn to methods for improving diabetes status in a subject in need of such improvement, wherein said methods comprise a step of identifying a β-2 adrenergic receptor gene allele.

Group II, claim(s) 1 and 3, drawn to methods for improving diabetes status in a subject in need of such improvement, wherein said methods comprise a step of identifying a β-3 adrenergic receptor gene allele.

Group III, claim(s) 1 and 4, drawn to methods for improving diabetes status in a subject in need of such improvement, wherein said methods comprise a step of identifying a peroxisome proliferator activator receptor γ gene allele.

Group IV, claim(s) 1 and 5, drawn to methods for improving diabetes status in a subject in need of such improvement, wherein said methods comprise a step of identifying a fatty acid binding protein gene allele.

Group V, claim(s) 1 and 6, drawn to methods for improving diabetes status in a subject in need of such improvement, wherein said methods comprise a step of identifying an insulin receptor substrate-1 gene allele.

2. The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature that joins these groups is the finding that in some subjects, certain alleles and/or a genotypes at a gene locus positively correlate with greater success in improving diabetes status in diabetic individuals, as compared with other alleles and/or genotypes at the same gene locus. However, this is not a "special technical feature" because it does not provide a contribution over the prior art, as required by PCT rule 13.2. Sakane *et al.* (Diabetes Care, Volume 20, Number 12, December 1997, pages 1887-1890) teach that patients without a Try64Arg mutation in the β_3-adrenergic receptor gene had larger decreases is a number of indicators of diabetic status after a weight loss program that included exercise as one component. Sakane *et al.* therefore teach that the Trp/Trp genotype is a genotype at a gene locus which positively correlates with greater success in improving diabetes status. Thus, Sakane *et al.* provide a method for improving diabetes status in a subject in need of such improvement, the method comprising: identifying a subject with diabetes having Trp/Trp genotype at codon 64 of the β_3-adrenergic receptor gene; and engaging the subject in exercise for a period of time sufficient to improve the diabetes status in the subject.

In light of the teaching of Sakane *et al.*, there is no special technical feature that joins these claims, and restriction is required as indicated. For each group, the special technical feature is the gene of interest in the claims. Claim 1 is included in all of the groups, and will be considered with any group that is elected.

3. During a telephone conversation with Dan Dazara on 5/6/02 a provisional election was made with traverse to prosecute the invention of group V, claims 1 and 6. Affirmation of this election must be made by applicant in replying to this Office action. Claims 2-5 and 7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The specification recites sequences, however, there is no paper copy of a sequence listing, no CRF, and no proper sequence identification numbers (see at least pages 7, 8, and 10).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit a CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the

specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method for improving diabetes status in a subject in need of such improvement, the method comprising a step of identifying a subject with diabetes or at risk of developing diabetes having an allele and/or genotype at a gene locus which positively correlates with greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus, and engaging the subject in exercise training for a period of time sufficient to improve the diabetes status in the subject. Thus, necessary for the practice of this invention is the identification of a nucleic acid whose presence is correlated with greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus. The specification has described only six genotypes that might meet this limitation, however, the data to support the assertion that even these six genotypes meet this limitation is weak, as is discussed in the 112 1st paragraph for lack of enablement description. Regardless, the genus of the invention of claim 1 is enormous,

encompassing any possible genotype of any possible gene or combination of genes that is associated with the recited phenotype. The specification has not provided any universal structural features that would unify this genus and demonstrate the possession of a genus of this breadth. This large genus is represented in the specification by at most six species, those particular genotypes recited in the claims. Thus, applicant has express possession of at most six species in a genus which comprises hundreds of millions of different possibilities.

However, even these species themselves do not appear to be adequately described in the specification because, although they are referred to as the "11" or "12" genotypes, the specification does not provide and description or definition as to what these codes represent. Therefore, even these six particular genotypes do not appear to be described in the specification. Claim 6 is drawn to a method for improving the diabetes status in a subject in need of such improvement, the method comprising a step of identifying a subject with diabetes or at risk of developing diabetes having a "12" genotype for an insulin receptor substrate-1 gene. This rejection applies to elected claim 6 because, although is limited to the detection of the "12" genotype in the insulin receptor substrate-1 gene, the specification does not describe what this genotype is.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The instant claims are not drawn to nucleic acids, per se, but they do require the specific knowledge of the presence or absence of particular nucleic acids for their practice. Thus, some

description of the nucleic acids whose genotypes is being detected is essential for the practice of the invention. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any methods within the scope of claim one other than those that are particularly described in the specification.

6. Claims 1and 6 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A restriction requirement in view of lack of unity of invention has been applied in this application. For the evaluation of enablement under 112 1st paragraph, the entire breadth of claim 1 and all of the examples have been considered.

Claim 1 is drawn to a method for improving diabetes status in a subject in need of such improvement, the method comprising a step of identifying a subject with diabetes or at risk of developing diabetes having an allele and/or genotype at a gene locus which positively correlates with greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus, and engaging the subject in exercise training for a period of time sufficient to improve the diabetes status in the subject. Thus, necessary for the practice of this invention is the identification of a nucleic acid whose presence is correlated with

greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus. Claim 6 is limited to the detection of the "12" genotype in the IRS-1 gene.

The prior art provides a number of mutations that are associated with diabetes, and in one case demonstrates that patients with a particular mutation have more success in improving glycemic control and insulin resistance after completing a weight loss program that includes exercise (Sakane *et al.*). Furthermore, the prior art provides methods for detecting the presence of particular mutations in patients with diabetes, for example the detection of the mutation that leads to the Gly972ARG mutation in the IRS-1 gene (Pedersen *et al.*). However, outside of the teachings of Sakane *et al.*, there is no teaching or suggestion in the prior art concerning alleles and/or genotypes at a gene locus which positively correlate with greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus.

The level of skill in the art of nucleic acid analysis and detection assays is quite high, but the unpredictability as to the presence of polymorphisms and their association with a particular phenotype is higher. It is unpredictable as to which alleles or genotypes might be indicators of greater success in improving diabetes status in diabetic individuals compared with other alleles and/or genotypes at the same locus. Neither the specification nor the prior art provide a universal method for determining a priori which genotypes would be useful in such a method.

The specification has described only six genotypes that might meet this limitation, however, the specification has failed to demonstrate that these genotypes are in fact correlated with greater success in improving diabetes status in a subject. The specification provides data

from tests in which eight to fifteen subjects were genotyped and then underwent exercise training. The subjects were measured for certain diabetic indicators before and after the exercise training. The specification provides the results of these experiments in tables 1, 2, and 3. However, no statistical tests were carried out to determine if the "trends" observed were in fact statistically significant observations. In each case, however, the sample sizes were quite small, and thus the observations lack any statistical power. For example, in the case of the elected invention (the detection of the "12" genotype in the IRS-1 gene), there were only two subjects that had the "12" genotype. There were nine subjects with the "11" genotype. The standard deviation in all three of the observed traits in the case of the "12" genotypes were quite large, and in two out of three cases the standard deviation was larger than the average value observed, indicating that the two subjects had dramatically different responses to exercise treatment. For all three observed diabetic indicators there is overlap between the range of response for the "11" genotype and for the "12" genotype. In light of these results, it appears that there is no demonstration that in fact the "12" genotype in the IRS-1 gene is correlated with greater success in improving diabetes status in diabetic individual compared with other alleles and/or genotypes at the same locus. A similar analysis might be applied to each of the examples in the specification, because in each case, the claims are supported by data that is drawn from experiments with very small sample sizes and has large amounts of variation for each comparison. Thus, no clear showing of a correlation between a particular genotype and greater success in improving diabetes status in diabetic individual compared with other alleles and/or genotypes at the same locus has been provided in the specification.

In order to practice the claimed invention for even any one of the disclosed embodiments, a significant amount of work would be required to be undertaken in order to reasonably confirm that an association exists between the recited phenotypes and an increased likelihood of improved diabetes status. In order to practice the claimed invention for an allele or a genotype that is outside of the disclosed examples, a larger amount of experimentation would be required that would involve the screening of patients for possible genotypes or alleles and then extensive experimentation to establish a relationship between such genotypes or alleles and the physical traits of interest. Such experimentation in itself would be inventive.

Thus, in light of these factors discussed herein, it is concluded that undue experimentation would be necessary to practice the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is rejected over the recitation "having a '12' genotype for an insulin receptor substrate-1 gene" because it is not clear from the claims or the specification what constitutes a '12' genotype. Although the specification refers to people having such a genotype, the specification never particularly identifies what alleles are present in patients designated as having this genotype.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 1 is rejected under 35 U.S.C. 102(a) and under 35 U.S.C. 102(a) as being anticipated by Sakane *et al.*

This rejection is being made under both 102(a) and 102(b). The instant filing date of this application is the date of the PCT filing, 11/23/99. This application also claims priority under 119 to a US provisional application 60/109432, filed 11/23/98. However, priority is not being granted back to the provisional filing date. While the provisional application discusses the preferred embodiments of this invention, the provisional application does not discuss or describe the general method claimed in claim 1. The provisional application only discusses the particular examples provided therein. There is no suggestion or statement that would support the broad claim of claim 1. Thus, this rejection is being made under 102(b). In the event that applicant is able to show that this claim is entitled to the 11/23/98 filing date, this reference is also available under 102(a), so this reference is being applied under both statutes.

Sakane *et al.* (Diabetes Care, Volume 20, Number 12, December 1997, pages 1887-1890) teach that patients without a Try64Arg mutation in the β_3-adrenergic receptor gene had larger decreases is a number of indicators of diabetic status after a weight loss program that included

exercise as one component. Sakane *et al.* therefore teach that the Trp/Trp genotype is a genotype at a gene locus which positively correlates with greater success in improving diabetes status. Thus, Sakane *et al.* provide a method for improving diabetes status in a subject in need of such improvement, the method comprising: identifying a subject with diabetes having Trp/Trp genotype at codon 64 of the β_3-adrenergic receptor gene; and engaging the subject in exercise for a period of time sufficient to improve the diabetes status in the subject.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen *et al.* (US 5827730) in view of Honkola *et al.* (Acta Diabetol. (1997) 34(4) 245-248).

Pedersen *et al.* teach a method that comprises identifying a subject with diabetes or at risk of developing diabetes having a genotype indicating the presence of a glycine972→arginine mutaiton for an insulin receptor substrate-1 gene (Col. 3, lines 10-12). It is noted that the claim specifics the identification of a "12" genotype, but it is unclear from the claims how such a mutation is defined. Thus, the teachings of Pedersen *et al.* are interpreted to meet the limitations of the first method step of the claim.

Pedersen *et al.* do not teach a method for improving diabetes status in a subject in need of such improvement that comprises engaging the subject in extensive exercise training for a period of time sufficient to improve the diabetes status in the subject.

Honkola *et al.* teach methods for improve diabetes status in subjects with diabetes that comprise engaging the subject in extensive exercise training for a period of time sufficient to improve the diabetes status in the subject.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have engaged a patient in extensive exercise after diagnosing the patient with diabetes using the method of Pederson *et al.*, and thus have achieved the method of claim 6. The ordinary practitioner would have been so motivated by the teachings of Honkola *et al.* since Honkola *et al.* teach that extensive exercise is associated with a significant improvement in long-term glycaemic control, and that "one must always keep in mind that any improvement of glycaemic control is of importance in order to avoid micro- and macrovascular complications."

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1634

May 22, 2002